

Office Action Summary	Application No. 09/663,968	Applicant(s) YIP, PING	
	Examiner KARLHEINZ R. SKOWRONEK	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 January 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 64,65,70,71,79,82,83,92 and 93 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 64-65, 70-71, 79, 82-83, and 92-93 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. <u>2010331</u> . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____. | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Claim Status

Claims 64-65, 70-71, 79, 82-83, and 92-93 are pending.

Claims 1-63, 66-69, 72-78, 80-81, and 84-91 are cancelled.

Claims 64-65, 70-71, 79, 82-83, and 92-93 have been examined.

Claims 64-65, 70-71, 79, 82-83, and 92-93 are rejected.

Priority

This application was filed on 19 September 2000 and does not claim priority to any earlier filed application.

Interview Summary

Applicant's representative was telephoned for interview as requested in the response dated 13 January 2010. Issues regarding claim 64 were indicated by the examiner. Examiner indicated a non-final action was being prepared comprising a new ground of rejection over art. Applicant's representative preferred that the grounds of rejection should be made of record and the office action sent.

Claim Rejections - 35 USC § 112

The rejection of claims 64, 65, and 71 as indefinite under 35 USC 112, second paragraph has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made below.

The rejection of claim 79 as indefinite under 35 USC 112, second paragraph is withdrawn in view of the amendments to the claims.

The rejection of claim 79 as lacking written description is withdrawn in view of the amendments to the claim.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Upon further search and reconsideration, the following rejections are newly applied.

Claims 64, 65, 70, and 71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 64 and 65 are unclear with respect to the step of compression of the intermediate data set. The metes and bounds of the claim are rendered indefinite by the lack in clarity. The claims are directed to an automated method of identifying a component in a DNA sample in which a mass spectrometer generates a data set; the data set is denoised and baseline corrected; putative peaks identified; a residual baseline generated; the residual baseline removed from the intermediate data set to generate a corrected data set; the putative peak is identified in the corrected data set; the component that corresponds to the putative peak is identified; the intermediate data is compressed to generate compressed data points that are real numbers having a whole portion representing a difference between two data values from the intermediate set. It is unclear what relationship is intended between the compressed data set and the

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process of identifying a component. It is unclear what role the step of compression has in the process.

Claim 70 is unclear with respect the removal of the Gaussian. The metes and bounds of the claim are rendered indefinite by the lack of clarity. The claim discloses that an area of twice the width of the Gaussian is removed from the left of center of each putative peak. The claim does not disclose at which point in the process the area of twice the width of the Gaussian is removed. It is unclear which step the removal of the area is associated, thus making the metes and bounds of the claim unclear.

Claim 71 is unclear with respect to the removal of an area of 50 Daltons from the right of center from each putative peak. The metes and bounds of the claim are rendered indefinite by the lack of clarity. Similar to claim 70, the claim does not disclose at which point in the process the area is removed or with which step the removal is associated. The claim is further unclear with respect to the area of 50 Daltons because the claim does not provide a measure of scale relative to the data and the area. The lack of a frame of reference for the area makes the removed area indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Upon further search and reconsideration, the following rejections are newly applied.

Claim 64 is rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125), in view of Ferrige et al. and in view of Leung et al. (Anal. Chem., Vol. 70, p. 5222-5229, 1998).

Claims 64 is directed to an automated method for identifying a component in a DNA sample using a mass spectrometer to generate a machine readable data set and analyzing the data by generating denoised data by performing noise reduction, correcting a baseline for the denoised data to generate an intermediate data set, defining peaks in the intermediate data set, subtracting the peaks from the intermediate data set to generate a residual data set, removing the residual data set from the intermediate data set to produce a corrected data set, locating peaks in the corrected data set, identifying the component that corresponds to each located peak, and compressing the intermediate data set so the compressed data comprises a real

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number with a whole portion representing a difference between two intermediate data points.

Green et al. teach a method, a computerized system, system, and machine-readable program operating on a computer for identifying a component in a DNA sample using a mass spectrometer (col. 5, line 18 to generate a machine readable data set and analyzing the data by performing noise reduction to generate denoised data, correcting a baseline for the denoised experimental data representing an intermediate data set, defining peaks in the intermediate data set as "fragment pattern" (col. 5, lines 9-43). Green et al. shows spectra can be "normalized" with fourth order polynomials (col. 11, line 36). Green et al. further teach the computer is integral to the instrument (col. 16, line 27-39).

Green et al. do not teach the removal of peaks and subsequent generation and removal of a residual baseline from the denoised experimental data.

Dunkel teach method of automated analysis and correction of spectral data obtained through ion cyclotron mass spectrometry (col. 1, lines 16-19). Dunkel shows that a mathematical model that describes the expected experimental spectral data is determined (col. 7, line 37-39). Dunkel shows that the best-fit mathematical model to the experimental data is subtracted from the experimental data to generate a residual (col. 9, line 10-13). Dunkel teach that the residual baseline obtained by removing peaks from experimental data can be applied to the experimental data to correct for baseline distortion (col. 11, lines 2-3). Dunkel teach the generation of a residual baseline by subtracting modeled peak data from the experimental "intermediate" data (col. 20, lines

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40-45). Dunkel teaches identifying includes identifying peak probabilities for the putative peak and is derived using signal to noise ratio (col.32, lines 27-29 and 48-51; and col. 33, lines 3 and 15-20). Dunkel shows baselines can be modeled as polynomial functions (col. 22, line58-61) Dunkel teach the modeling of peaks by fitting a Gaussian curve (col. 8, lines 5-7). Dunkel teach performing a mass shift of the peak position (col. 2, lines 43-46).

Green et al. in view of Dunkel does not show a step of data compression.

Ferrige et al. shows a mass spectrum deconvolution method called the maximum entropy (MaxEnt) technique. Ferrige et al. shows the MaxEnt technique compresses the intermediate data (p. 376, col. 2). Ferrige et al. shows that the MaxEnt technique is able to deconvolve noisy data much more effectively (p.374, col. 2). Ferrige et al. shows that the MaxEnt technique successfully enabled severely resolved peaks to be totally resolved (p. 377, col. 2).

Leung et al. shows that wavelet transforms are a technique of data compression (p. 5222, col. 2). Leung et al. shows that the compressed data is a real number that has a whole portion representing a difference between two data points (p. 5224, col. 1). Leung et al. shows the major advantage of the proposed method is that it can perform numerical differentiation and noise reduction in the same calculation and can enhance the signal-to-noise ratio (SNR) for even higher order derivatives (p. 5222, col. 2).

It would have been obvious to one of skill in the art to combine the method for correction of spectral data of Dunkel with the method intermediate data set generation of Green et al. because Green et al. teach that other signal processing techniques can

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be applied to generate clean, corrected data (col. 5, lines 47-49) and Dunkel teaches that baseline correction can be corrected by subtracting the residual baseline. It would have been further obvious to one of ordinary skill in the art at the time of invention to modify the method of identifying a component in a sample using a mass spectrometer of Green et al. in view of Dunkel with the MaxEnt deconvolution technique that compresses data of Ferrige et al. because Ferrige et al. shows that the MaxEnt technique is able to deconvolve noisy data much more effectively which successfully enabled severely resolved peaks to be totally resolved. It would have been further obvious to one of ordinary skill in the art to modify the method of identifying a component in a sample using a mass spectrometer of Green et al. in view of Dunkel and in view of Ferrige et al. with the wavelet transform technique for data compression of Leung et al. because Leung et al. shows the major advantage of the proposed method is that it can perform numerical differentiation and noise reduction in the same calculation and can enhance the signal-to-noise ratio (SNR) for even higher order derivatives.

Claims 79 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125), and in view of Croft et al. (Journal of Biomolecular NMR, Vol. 10, p. 207–219, 1997).

Claim 79 is directed to an automated method for identifying a component in a DNA sample using a mass spectrometer to generate a machine readable data set and analyzing the data by generating denoised data by performing noise reduction,

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correcting a baseline for the denoised data to generate an intermediate data set, defining peaks in the intermediate data set, subtracting the peaks from the intermediate data set to generate a residual data set, removing the residual data set from the intermediate data set to produce a corrected data set, locating peaks in the corrected data set, identifying the component that corresponds to each located peak in which a peak probability is determined and the peak probability is multiplied by a penalty to produce a final probability. Claim 92 is directed to determining a peak probability from a profile.

Green et al. teach a method for identifying a component in a DNA sample using a mass spectrometer (col. 5, line 18 to generate a machine readable data set and analyzing the data by performing noise reduction to generate denoised data, correcting a baseline for the denoised experimental data representing an intermediate data set, defining peaks in the intermediate data set as "fragment pattern" (col. 5, lines 9-43). Green et al. shows spectra can be "normalized" with fourth order polynomials (col. 11, line 36). Green et al. further teach the computer is integral to the instrument (col. 16, line 27-39).

Green et al. do not teach the removal of peaks and subsequent generation and removal of a residual baseline from the denoised experimental data.

Dunkel teach method of automated analysis and correction of spectral data obtained through ion cyclotron mass spectrometry (col. 1, lines 16-19). Dunkel shows that a mathematical model that describes the expected experimental spectral data is determined (col. 7, line 37-39). Dunkel shows that the best-fit mathematical model to the

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experimental data is subtracted from the experimental data to generate a residual (col. 9, line 10-13). Dunkel teach that the residual baseline obtained by removing peaks from experimental data can be applied to the experimental data to correct for baseline distortion (col. 11, lines 2-3). Dunkel teach the generation of a residual baseline by subtracting modeled peak data from the experimental "intermediate" data (col. 20, lines 40-45). Dunkel teaches identifying includes identifying peak probabilities for the putative peak and is derived using signal to noise ratio (col.32, lines 27-29 and 48-51; and col. 33, lines 3 and 15-20). Dunkel shows baselines can be modeled as polynomial functions (col. 22, line 58-61) Dunkel teach the modeling of peaks by fitting a Gaussian curve (col. 8, lines 5-7). Dunkel teach performing a mass shift of the peak position (col. 2, lines 43-46).

Green et al. in view of Dunkel does not show determining a peak probability.

Croft et al. shows a method of automated peak assignment from spectrometer data. Croft shows that identifying putative peak comprises determining a peak probability (p. 208, col. 2-p. 209, col.1). Croft et al. shows the peak probability is multiplied by a penalty to obtain a final peak probability that is used to filter peaks of high interest from peaks of lower interest (p. 211, col. 1). Croft et al. shows the application of a "peak profile" of expected peaks used to determine peak probability (p. 209, col. 1). Croft et al. shows filtering peaks by peak probability advantageously reduces large lists of peaks to a manageable size and ensures that the correct results are more likely to be the highest scoring ones (p. 211, col. 1).

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It would have been obvious to one of skill in the art to combine the method for correction of spectral data of Dunkel with the method intermediate data set generation of Green et al. because Green et al. teach that other signal processing techniques can be applied to generate clean, corrected data (col. 5, lines 47-49) and Dunkel teaches that baseline correction can be corrected by subtracting the residual baseline. It would have been further obvious to one of ordinary skill in the art at the time of invention to modify the method of identifying a component in a sample using a mass spectrometer of Green et al. in view of Dunkel with the method of peak filtering based on penalized peak probabilities of Croft et al. because Croft et al. shows filtering peaks by peak probability advantageously reduces large lists of peaks to a manageable size and ensures that the correct results are more likely to be the highest scoring ones.

Claim 82-83 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green et al. (US PAT 5, 853,979), in view of Dunkel (US PAT 5,572,125), in view of Croft et al. (Journal of Biomolecular NMR, Vol. 10, p. 207–219, 1997) as applied to claim 79 and 92 above, and further in view of Mir et al.(Annual review of Genomics and Human Genetics Vol. 1, 329-360, 2000).

Claim 82 is directed to an automated method for identifying a component in a DNA sample using a mass spectrometer to generate a machine readable data set and analyzing the data by generating denoised data by performing noise reduction, correcting a baseline for the denoised data to generate an intermediate data set, defining peaks in the intermediate data set, subtracting the peaks from the intermediate

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data set to generate a residual data set, removing the residual data set from the intermediate data set to produce a corrected data set, locating peaks in the corrected data set, identifying the component that corresponds to each located peak in which a peak probability is determined and comparing the highest peak probability to the next highest probability to determine a calling ratio. Claim 83 is directed to using the calling ratio to determine if a sample will be called. Claim 93 is directed to assigning the allelic penalty to the allelic ratio.

Green et al. teach a method for identifying a component in a DNA sample using a mass spectrometer (col. 5, line 18 to generate a machine readable data set and analyzing the data by performing noise reduction to generate denoised data, correcting a baseline for the denoised experimental data representing an intermediate data set, defining peaks in the intermediate data set as "fragment pattern" (col. 5, lines 9-43). Green et al. shows spectra can be "normalized" with fourth order polynomials (col. 11, line 36). Green et al. further teach the computer is integral to the instrument (col. 16, line 27-39).

Green et al. do not teach the removal of peaks and subsequent generation and removal of a residual baseline from the denoised experimental data.

Dunkel teach method of automated analysis and correction of spectral data obtained through ion cyclotron mass spectrometry (col. 1, lines 16-19). Dunkel shows that a mathematical model that describes the expected experimental spectral data is determined (col. 7, line 37-39). Dunkel shows that the best-fit mathematical model to the experimental data is subtracted from the experimental data to generate a residual (col.

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9, line 10-13). Dunkel teach that the residual baseline obtained by removing peaks from experimental data can be applied to the experimental data to correct for baseline distortion (col. 11, lines 2-3). Dunkel teach the generation of a residual baseline by subtracting modeled peak data from the experimental "intermediate" data (col. 20, lines 40-45). Dunkel teaches identifying includes identifying peak probabilities for the putative peak and is derived using signal to noise ratio (col.32, lines 27-29 and 48-51; and col. 33, lines 3 and 15-20). Dunkel shows baselines can be modeled as polynomial functions (col. 22, line58-61) Dunkel teach the modeling of peaks by fitting a Gaussian curve (col. 8, lines 5-7). Dunkel teach performing a mass shift of the peak position (col. 2, lines 43-46).

Green et al. in view of Dunkel does not show determining a peak probability.

Croft et al. shows a method of automated peak assignment from spectrometer data. Croft shows that identifying putative peak comprises determining a peak probability (p. 208, col. 2-p. 209, col.1). Croft et al. shows the peak probability is multiplied by a penalty to obtain a final peak probability that is used to filter peaks of high interest from peaks of lower interest (p. 211, col. 1).Croft et al. shows the application of a "peak profile" of expected peaks used to determine peak probability (p. 209, col. 1).Croft et al. shows filtering peaks by peak probability advantageously reduces large lists of peaks to a manageable size and ensures that the correct results are more likely to be the highest scoring ones (p. 211, col. 1).

Green et al. in view of Dunkel in view of Croft et al. do not show a calling ratio.

Mir et al. shows methods for the large scale analysis of sequence variation in genes and genomic DNA. Mir et al. shows that a calling ratio is determined by comparing the highest peak to the next highest peak (p. 338). Mir et al. shows that owing to imperfect discrimination, thresholds have to be set to accept or reject a signal, reading on an allelic penalty (p. 338). Mir et al shows the calling ratio is used to determine if the sample will be called (p. 338). Mir et al. shows that allelic variation is advantageously determined in the ratiometric changes in hybridization pattern of peak intensity (p. 337-338).

It would have been obvious to one of skill in the art to combine the method for correction of spectral data of Dunkel with the method intermediate data set generation of Green et al. because Green et al. teach that other signal processing techniques can be applied to generate clean, corrected data (col. 5, lines 47-49) and Dunkel teaches that baseline correction can be corrected by subtracting the residual baseline. It would have been further obvious to one of ordinary skill in the art at the time of invention to modify the method of identifying a component in a sample using a mass spectrometer of Green et al. in view of Dunkel with the method of peak filtering based on penalized peak probabilities of Croft et al. because Croft et al. shows filtering peaks by peak probability advantageously reduces large lists of peaks to a manageable size and ensures that the correct results are more likely to be the highest scoring ones. It would have been further obvious to one of ordinary skill in the art to modify the method of identifying a component in a sample using a mass spectrometer of Green et al. in view of Dunkel and the method of peak filtering based on penalized peak probabilities of Croft et al.

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with the determination of a calling ratio of Mir et al. because Mir et al. shows that allelic variation is advantageously and successfully determined in the ratiometric changes in hybridization pattern of peak intensity.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571)272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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